Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Digestive and Liver Disease 53 (2021) 153–157

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Meta-Analysis

Metabolic associated fatty liver disease increases the severity of COVID-19: A meta-analysis

Lu Pan[a], Pan Huang[b,*], Xia Xie[c,*], Jiachen Xu[d], Dawei Guo[e], Yuan Jiang[f]

[a] Department of Critical Care Unit, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, No. 3002, Sungang west Road, Futian District, Shenzhen, China
[b] College of Nursing, Gannan Medical University, No. 1 Hexie Road, Rongjiang New area, Ganzhou, China
[c] College of Nursing, North Sichuan Medical College, No. 234, Fujiang Road, Shunqing District, Nanchong City, Sichuan, China
[d] Department of medicine, JingGangshan University,Ji'an,Jiangxi province,China, No.28 Xueyuan Road, Qingyuan District, Ji 'an City, China
[e] Department of medicine, JingGangshan University,Ji'an,Jiangxi province,China, No.28 Xueyuan Road, Qingyuan District, Ji 'an City, China
[f] Department of medicine, JingGangshan University, Ji'an,Jiangxi province,China, No.28 Xueyuan Road, Qingyuan District, Ji 'an City, China

ARTICLE INFO

Article history:
Received 21 July 2020
Accepted 7 September 2020
Available online 17 September 2020

Keywords:
COVID-19
SARS-CoV-2
Metabolic associated fatty liver disease

ABSTRACT

Background: The association between metabolic-associated fatty liver disease (MAFLD) and disease progression in patients with the coronavirus disease 2019 (COVID-19) are unclear.
Aims: To explore the association between MAFLD and the severity of COVID-19 by meta-analysis.
Methods: We conducted a literature search using PubMed, EMBASE, Medline (OVID), and MedRxiv from inception to July 6, 2020. Newcastle-Ottawa Scale (NOS) and Stata 14.0 were used for quality assessment of included studies as well as for performing a pooled analysis.
Results: A total of 6 studies with 1,293 participants were included after screening. Four studies reported the prevalence of MAFLD patients with COVID-19, with a pooled prevalence of 0.31 for MAFLD (95CI 0.28, 0.35, $I^2 = 38.8\%$, $P = 0.179$). MAFLD increased the risk of COVID-19 disease severity, with a pooled OR of 2.93 (95CI 1.87, 4.60, $I^2 = 34.3\%$, $P = 0.166$).
Conclusion: In this meta-analysis, we found that a high percentage of patients with COVID-19 had MAFLD. Meanwhile, MAFLD increased the risk of disease progression among patients with COVID-19. Thus, better intensive care and monitoring are needed for MAFLD patients infected by SARS-COV-2.

1. Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 23 million confirmed cases and 800 thousand deaths worldwide as of August 24, 2020 (https://covid19.who.int/). Emerging data suggest that hypertension, diabetes, and cardiovascular diseases (CVDs) are highly prevalent among patients hospitalized with COVID-19, and that these may be associated with an increased risk of mortality due to the virus. Metabolic associated fatty liver disease (MAFLD) is a well-known risk factor for CVDs and diabetes, and has been closely related to mortality due to these diseases [1,2]. MAFLD was reported to affect approximately 20–30% of people worldwide [3-5]. Several studies demonstrated that MAFLD could increase disease severity in patients with COVID-19. However, Zhou et al. found that MAFLD was not significantly associated with a higher risk of disease severity in young patients [6]. Therefore, in order to clarify the role of MAFLD among patients with COVID-19, we conducted a meta-analysis to summarize the existing evidence about the pooled prevalence of MAFLD, as well as the association between MAFLD and disease severity among patients with COVID-19.

2. Methods

2.1. Search strategy

We conducted a literature search using PubMed, EMBASE, Medline(OVID), and MedRxiv from inception to July 6, 2020. We used keywords and MeSH terms to retrieve potential suitable papers, including "SARS-COV-2", "COVID-19", "metabolic associated fatty liver disease", "nonalcoholic fatty liver disease (NAFLD)", and "nonalcoholic steatohepatitis (NASH)". The detail of the search strategy used is shown in the *Supplementary information.*

* Corresponding authors.
E-mail addresses: gnyxywthp@163.com, gnyxywthx@163.com (P. Huang), 583564979@qq.com (X. Xie).

https://doi.org/10.1016/j.dld.2020.09.007
1590-8658/

2.2. Study selection

We screened the titles and abstracts of papers. For potential eligible papers, we obtained the full text. The progression of screening was determined independently by (Pan Lu and Xia Xie). Disagreements were resolved through further discussions or third-party arbitration.

2.3. Eligibility criteria

We included studies investigating the association between MAFLD and disease severity among patients with COVID-19. We excluded studies when it was a review or if the study was not in English. MAFLD was defined by criteria based on hepatic steatosis, in addition to meeting one of the following clinical parameters, such as being overweight, having type 2 diabetes mellitus, or exhibiting metabolic dysregulation [5,7]. All of studies evaluated the severity of COVID-19 according to the criteria in Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Patients were regarded as severe cases when they meet any of following conditions: (i)significantly increased respiration rate; (ii)hypoxia; (iii)consciousness disorders: apathy, somnolence, coma, and convulsions; (iv)food refusal or feeding difficulty and dehydration; (v)other manifestations: such as bleeding and coagulation disorders, myocardial damage, gastrointestinal dysfunction, raised level of liver enzyme, and rhabdomyolysis; (vi)critical cases [8].

2.4. Data extraction

Two authors (Xia Xie and Jiang Yuan) independently extracted the following information from the included studies: country, investigation time, age, study design, sample number, percentage of males, and prevalence of MAFLD.

2.5. Quality assessment of the included studies

Study quality was independently performed by (Jiachen Xu and Dawei Guo) using the Newcastle-Ottawa Scale (NOS). The NOS scale for cross-sectional studies includes selection, comparability, and outcome. A high score indicates a high quality.

2.6. Statistical analysis

We performed pooled analysis using Stata 14.0 (Stata Corp, College Station, TX). A fixed effects model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the association between MAFLD and disease severity among patients with COVID-19. Heterogeneity was examined using the I^2 value and Cochran's Q test. A lower I^2 value indicated lower heterogeneity. We also

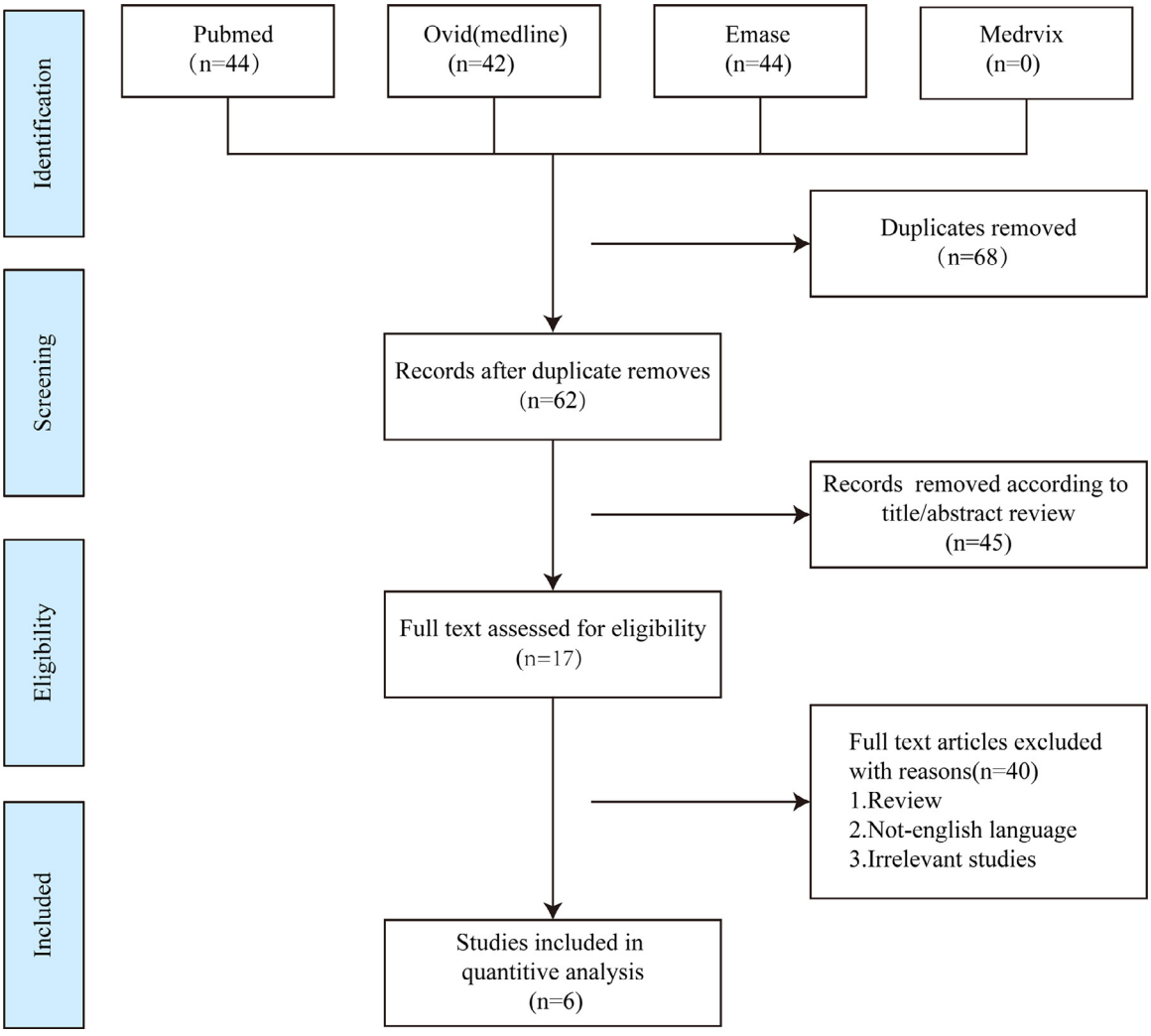

Fig. 1. The flowchart of research screening.

Table 1
The characteristics of the included studies.

Study	Region	Age	Sample	Study design	Male	MAFLD%	NOS score
Zhou Y(a) 2020	China	–	327	cross-sectional study	–	28.4%	9
Zhou YJ(b) 2020	China	42.1 ± 11.4	101	case-control study	0.745	–	8
Targher G 2020	China	47	310	cross-sectional study	0.481	30.3%	8
Ji D 2020	China	44.5(34.8–54.1)	202	cross-sectional study	0.559	37.6%	9
Zheng K 2020	China	47	214	cross-sectional study	0.258	30.8%	8
Gao F 2020	China	46.0 ± 13.0	130	case-control study	0.631	–	9

Abbreviations:NOS, Newcastle-Ottawa Scale; MAFLD, Metabolic associated fatty liver disease;.

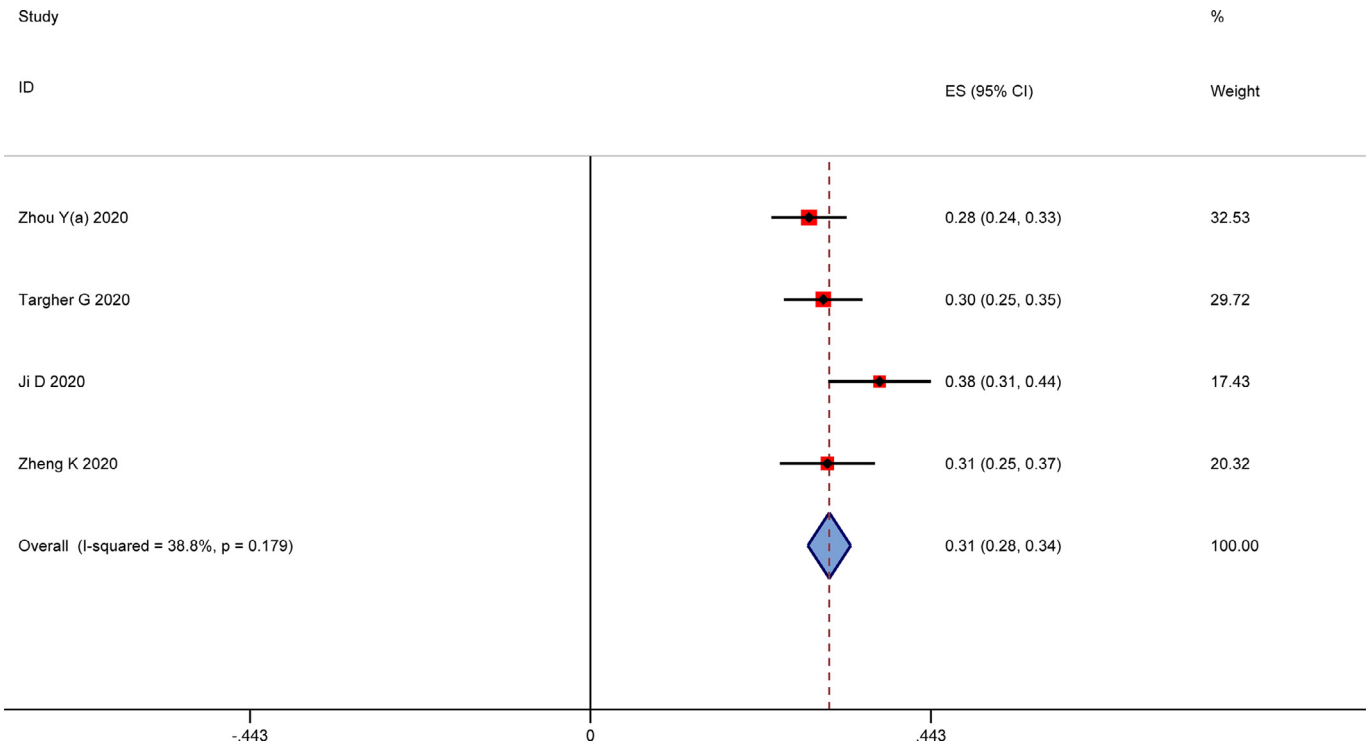

Fig. 2. The pooled prevalence of MAFLD among patients with COVID-19.

calculated the pooled prevalence of MAFLD among patients with COVID-19.

3. Results

3.1. Included studies

A total of 6 studies with 1293 participants were included after screening (Fig. 1) [1,6,9-12]. All of these studies were performed in China, and included four cross-sectional studies and two case-control studies (Table 1). All studies evaluated the severity of COVID-19 according to the criteria listed in the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). The NOS score ranged from 8 to 9 (Table S1–2).

3.2. The pooled prevalence of MALFD among patients with COVID-19

Four studies reported the prevalence of MAFLD patients with COVID-19, with pooled prevalence of MAFLD found to be 0.31(95CI 0.28, 0.35, I^2=38.8%, P = 0.179) (Fig. 2).

3.3. MALFD increases the risk of disease severity among patients with COVID-19

Six studies investigated the association between MAFLD and disease severity risk in patients with COVID-19. MAFLD increased the risk of COVID-19 disease severity, with a pooled OR of 2.93 (95CI 1.87, 4.60, I^2=34.3%, P = 0.166) (Fig. 3).

4. Discussion

In the present study, patients with COVID-19 had high percentage of MAFLD, with MAFLD found to increase the risk of disease progression in patients with COVID-19. MAFLD was defined by criteria based on hepatic steatosis, in addition to metabolic diseases, these studies had a high percentage among patients with COVID-19. For instance, Richardson et al. reported a prevalence of 41.7% for obesity and 33.8% for diabetes among 5700 patients with COVID-19 in New York [13]. Meanwhile, metabolic diseases were significantly associated with adverse clinical outcomes in patients with COVID-19 [14-16]. Recently, several meta-analyses demonstrated that diabetes and obesity were associated with increased risk for mortality and disease severity of COVID-19 [17,18].

For COVID-19 infection to occur, SARS-CoV-2 must bind to the host cell surface's ACE2 receptor, which initiates the host defense response and disease process [19,20]. The expression of ACE2 was higher in the animal model of hepatic steatosis [21], which may increase the risk of SARS-CoV-2 entry into the hepatocytes, thus leading to liver injury. Meanwhile, liver injury was reported to be significantly associated with an increased risk of mortality among patients with COVID-19 [22-24]. In addition, patients with MAFLD were characterized by impaired hepatic innate

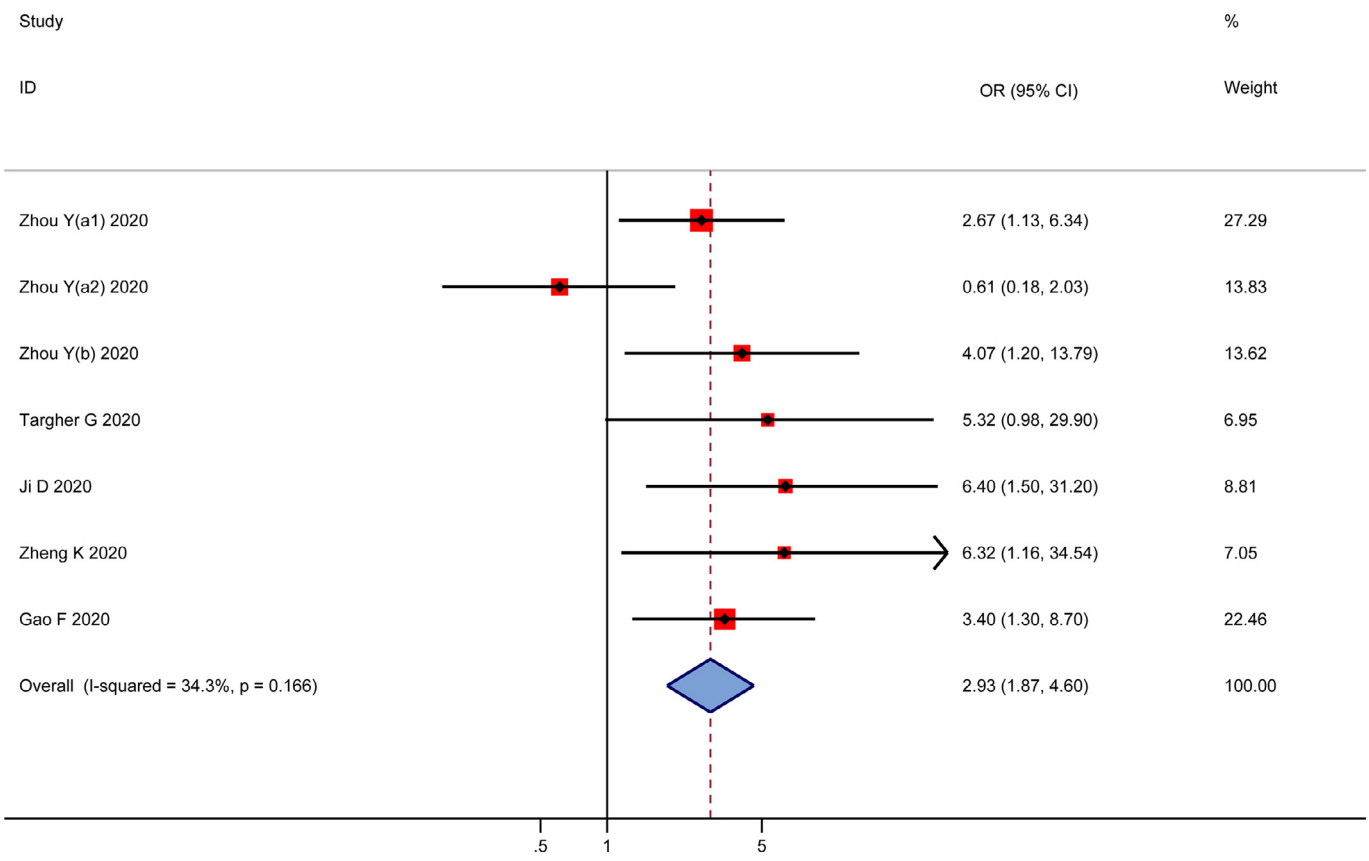

Fig. 3. The association of MAFLD with disease severity among patients with COVID-19.

immunity, such as having macrophage in polarization stages, as well as exhibiting increased levels of inflammatory mediators and cytokines [25,26]. Therefore, the status of inflammation associated with MAFLD further exacerbates the infection in patients with COVID-19 and can even lead to a cytokine storm, which greatly increases mortality risk.

There are several limitations in our present study. First, the sample number included studies which were small and conducted only in China, which may have affected the extrapolation of the results. Fortunately, we conducted retrieval of systematic references using several open databases and medRxiv. However, the results still need to be further validated using large-scale studies involving a variety of regions and races. Second, there were only six studies included in our final analysis, with only one study having a sub-group analysis, which may have impacted our pooled results. Nevertheless, the heterogeneity of the studies was reasonably acceptable, thus ensuring the reliability of outcomes in the studies. Finally, the included studies were cross-sectional studies and case-control studies, which are considered to be inferior to prospective cohort studies.

In conclusion, patients with COVID-19 had high percentage of MAFLD. In addition, MAFLD increased the risk of disease progression in patients with COVID-19. Thus, better intensive care and monitoring are needed for MAFLD patients infected by SARS-COV-2.

Sources of funding, grant support

None

Financial disclosure

None

Declaration of Competing Interest

No potential conflicts of interest were disclosed.

Acknowledgements

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2020.09.007.

References

[1] Gao F, Zheng KI, Wang XB, et al. Metabolic associated fatty liver disease increases coronavirus disease 2019 disease severity in nondiabetic patients. J Gastroenterol Hepatol 2020.
[2] Ciardullo S, Monti T, Perseghin G. Prevalence of liver steatosis and fibrosis detected by transient elastography in adolescents in the 2017-2018 national health and nutrition examination survey. Clin Gastroenterol Hepatol: Off Clin Pract J Am Gastroenterol Assoc 2020.
[3] Zhou F, Zhou J, Wang W, et al. Unexpected rapid increase in the burden of NAFLD in China from 2008 to 2018: a systematic review and meta-analysis. Hepatology (Baltimore, Md) 2019;70:1119–33.
[4] Zhou J, Zhou F, Wang W, et al. Epidemiological features of NAFLD from 1999 to 2018 in China. Hepatology (Baltimore, Md) 2020;71:1851–64.
[5] Eslam M, Sanyal AJ, George J. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158:1999–2014.e1.
[6] Zhou YJ, Zheng KI, Wang XB, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. J Hepatol 2020;73:719–21.
[7] Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202–9.
[8] Miao H, Li H, Yao Y, et al. Update on recommendations for the diagnosis and treatment of SARS-CoV-2 infection in children. Eur J Clin Microbiol Infect Dis: Off Publ Eur Soc Clin Microbiol 2020:1–13.

[9] Zhou YJ, Zheng KI, Wang XB, et al. Metabolic-associated fatty liver disease is associated with severity of COVID-19. Liver Int: Off J Int Assoc Study Liver 2020.
[10] Targher G, Mantovani A, Byrne CD, et al. Detrimental effects of metabolic dysfunction-associated fatty liver disease and increased neutrophil-to-lymphocyte ratio on severity of COVID-19. Diabetes Metab 2020.
[11] Zheng KI, Gao F, Wang XB, et al. Letter to the Editor: obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. Metab Clin Exp 2020;108:154244.
[12] Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol 2020;73:451–3.
[13] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323:2052–9.
[14] Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;31 1068-77.e3.
[15] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
[16] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
[17] Yang J, Hu J, Zhu C. Obesity aggravates COVID-19: a systematic review and meta-analysis. J Med Virol 2020.
[18] Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 2020;14:395–403.
[19] Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 2020;581:215–20.
[20] Wang Q, Zhang Y, Wu L, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell 2020;181:894–904.e9.
[21] Zhang W, Li C, Liu B, et al. Pioglitazone upregulates hepatic angiotensin converting enzyme 2 expression in rats with steatohepatitis. Ann Hepatol 2013;12:892–900.
[22] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5:428–30.
[23] Phipps MM, Barraza LH, LaSota ED, et al. Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large US cohort. Hepatology (Baltimore, Md) 2020.
[24] Lei F, Liu YM, Zhou F, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. Hepatology (Baltimore, Md) 2020.
[25] Kazankov K, Jørgensen SMD, Thomsen KL, et al. The role of macrophages in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Nat Rev Gastroenterol Hepatol 2019;16:145–59.
[26] Musso G, Cassader M, Gambino R. Non-alcoholic steatohepatitis: emerging molecular targets and therapeutic strategies. Nat Rev Drug Discov 2016;15:249–74.